international biobank and cohort studies:developing a harmonious approach

david moher, department of pediatrics, faculty of medicine, university of ottawa; clinical epidemiology program, children's hospital of eastern ontario research institute, ottawa

introduction to the
CONSORT/STROBE concept, and
extension to biobank studies


MAC
Money Access Center

randomized trials

- the most expensive form of healthcare evaluation
  - can easily cost $1 million to $50 million
  - > 40,000 ongoing rcts
- accounts for less than 10% of the published healthcare literature

quality of reports of randomized trials

- reviewed 2000 randomized trials of all treatments for schizophrenia
  - only 4% (n=80) of the trials clearly described the methods of allocation
- reviewed 122 randomized trials of SSRIs for depression
  - only 1 had an adequate description of randomization
- reviewed 279 randomized trials of head injury
  - 47 (23%) reported on the method of allocation concealment

Thornley B, Adams CE. Content and quality of 2000 controlled trials in schizophrenia over 50 years. British Medical Journal 1998;317:1181-1184

Hotopf M, Lewis G, Normand C. Putting trials on trial - the costs and consequences of small trials in depression: a systematic review of methodology. *J*ournal of Epidemiology and Community Health 1997;51:354-358

Dickinson K, Bunn F, Wentz R, Edwards P, Roberts I. Size and quality of randomised controlled trials in head injury: review of published studies. BMJ 2000;320:1308-1311

does low quality matter?

exaggerate the estimates
of an intervention's effectiveness?

adequate allocation concealment

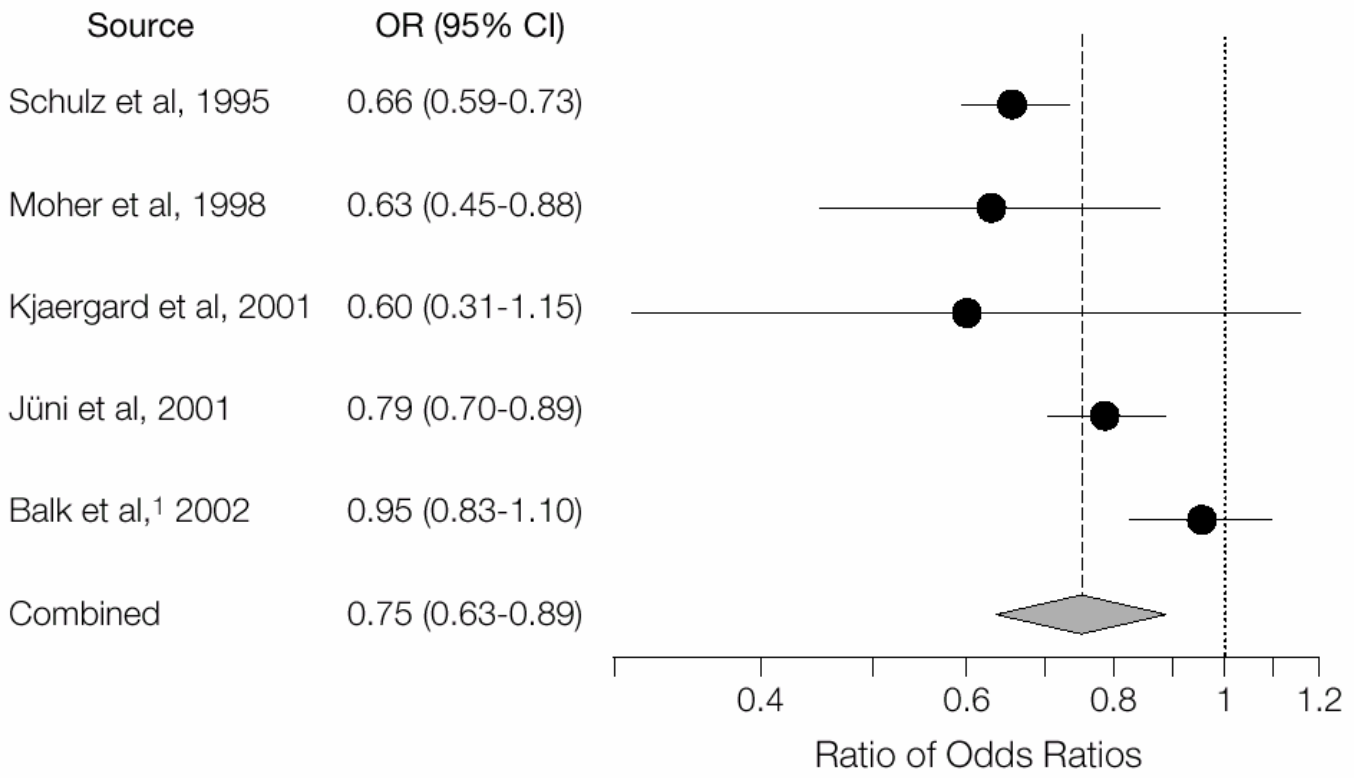
- a technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment
- allocation concealment prevents researchers from (unconsciously or otherwise) influencing which participants are assigned to a given intervention group
- possible in every randomized trial unlike other techniques, such as blinding

importance of allocation concealment

inadequately concealed trials, compared to adequately concealed ones, exaggerate the estimates of an intervention's effectiveness by 30%, on average.

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-412

Figure. Comparison of Treatment Effect Estimates From Trials With Inadequate or Unclear Allocation Concealment With Adequately Concealed Trials



developing an international standard for reporting randomized trials

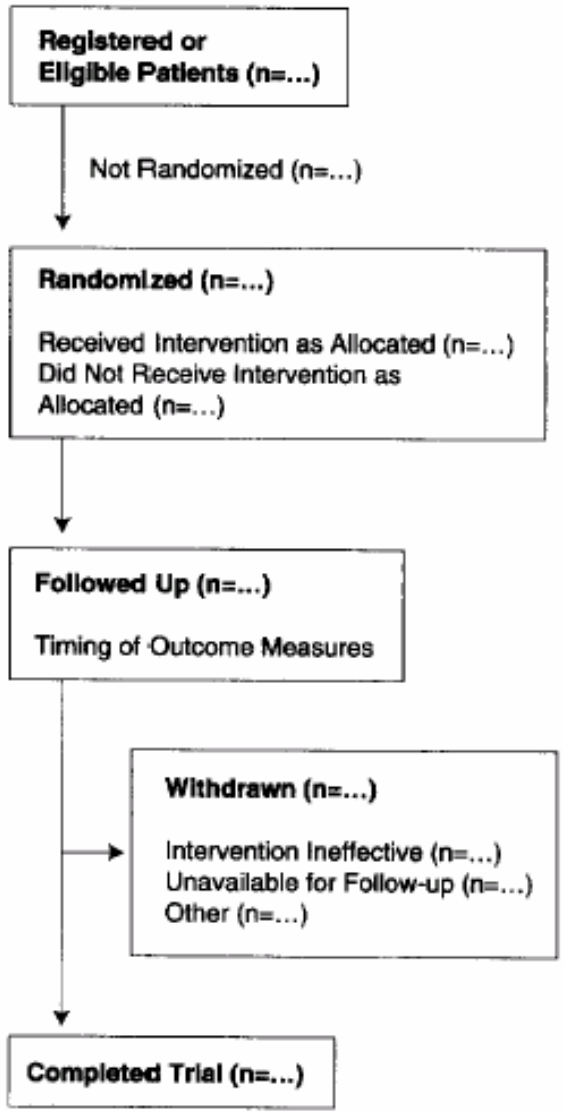
CONSORT

history of CONSORT (consolidated standards of reporting trials)

- started with the standards of Reporting Trials (SORT) meeting in 1993, in ottawa
  - clinical trialists, methodologists and biomedical editors

Checklist to Be Used by Authors When Preparing or by Readers When Analyzing a Report of a Randomized Controlled Trial

Item	Yes	No	Unable to Determine
1. State the unit of assignment.	☐	☐	☐
2. State the method used to generate the intervention assignment schedule.	☐	☐	☐
3. Describe the method used to conceal the intervention assignment schedule from participants and clinicians until recruitment was complete and irrevocable.	☐	☐	☐
4. Describe the method(s) used to separate the generator and executor of the assignment.	☐	☐	☐
5. Describe an auditable process of executing the assignment method.	☐	☐	☐
6. Identify and compare the distributions of important prognostic characteristics and demographics at baseline.	☐	☐	☐
7. State the method of masking.	☐	☐	☐
8. State how frequently care providers were aware of the intervention allocation, by intervention group.	☐	☐	☐
9. State how frequently participants were aware of the intervention allocation, by intervention group.	☐	☐	☐
10. State whether (and how) outcome assessors were aware of the intervention allocation, by intervention group.	☐	☐	☐
11. State whether the investigator was unaware of trends in the study at the time of participant assignment.	☐	☐	☐
12. State whether masking was successfully achieved for the trial.	☐	☐	☐
13. State whether the data analyst was aware of intervention allocation.*	☐	☐	☐
14. State whether individual participant data were entered into the trial database without awareness of intervention allocation.	☐	☐	☐
15. State whether the data analyst was masked to intervention allocation.	☐	☐	☐
16. Describe fully the numbers and flow of participants, by intervention group, throughout the trial.	☐	☐	☐
17. State clearly the average duration of the trial, by intervention group, and the start and closure dates for the trial.†	☐	☐	☐
18. Report the reason for dropout clearly, by intervention group.	☐	☐	☐
19. Describe the actual timing of measurements, by intervention group.	☐	☐	☐
20. State the predefined primary outcome(s) and analyses clearly.	☐	☐	☐
21. Describe clearly whether the primary analysis has used the intention-to-treat principle.	☐	☐	☐
22. State the intended sample size and its justification.	☐	☐	☐
23. State and explain why the trial is being reported now.	☐	☐	☐
24. Describe and/or compare trial dropouts and completers.	☐	☐	☐
25. State or reference the reliability, validity, and standardization of the primary outcome.‡	☐	☐	☐
26. Define what constituted adverse events and how they were monitored by intervention group.	☐	☐	☐
27. State the appropriate analytical techniques applied to the primary outcome measure(s).	☐	☐	☐
28. Present appropriate measures of variability (eg, confidence intervals for primary outcome measures).	☐	☐	☐
29. Present sufficient simple (unadjusted) summary data on primary outcome measures and important side effects so that the reader can reproduce the results.	☐	☐	☐
30. State the actual probability value and the nature of the significance test.	☐	☐	☐
31. Present appropriate interpretations (eg, NS, no effect; $P<.05$, proof).	☐	☐	☐
32. Present the appropriate emphasis in displaying and interpreting the statistical analysis, in particular controlling for unplanned comparisons	☐	☐	☐



Flow diagram of how participants can be represented passing through the various stages of a trial, including withdrawals and timing of outcome measurements.

history of CONSORT (consolidated standards of reporting trials)

- experiment with publication of rct
  - Williams JW, Holleman DR, Samsa GP, Simel DL. Randomized controlled trial of three versus ten days of trimethoprim/sulamethoxazole for acute maxillary sinusitis. JAMA 1995;273:1015-21
    - difficult to use

concurrently

- working group on recommendations for reporting clinical trials in the biomedical literature - asilomar group
- jama editorial (rennie)
- chicago, o’hare hilton, 1995

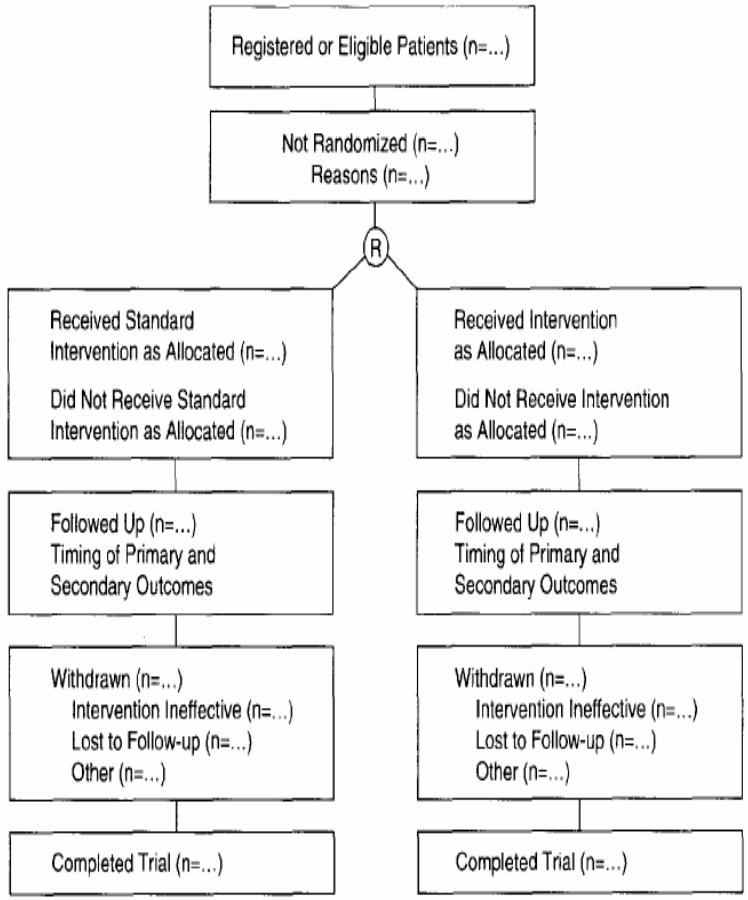
Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz K, Simel D, Stroup D. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. Journal of the American Medical Association. 1996;276:637-639.

‘original’ CONSORT statement

checklist and flow diagram

Consolidation of Standards for Reporting Trials—CONSORT[3,4]

Heading	Subheading	Descriptor	Was It Reported?	On What Page No.?
Title		Identify the study as a randomized trial.[7]		
Abstract		Use a structured format.[8,9]		
Introduction		State prospectively defined hypothesis, clinical objectives, and planned subgroup or covariate analyses.[10]		
Methods				
	Protocol	Describe Planned study population, together with inclusion/exclusion criteria. Planned interventions and their timing. Primary and secondary outcome measure(s) and the minimum important difference(s), and indicate how the target sample size was projected.[2,11] Rationale and methods for statistical analyses, detailing main comparative analyses and whether they were completed on an intention-to-treat basis.[12,13] Prospectively defined stopping rules (if warranted).[14]		
	Assignment	Describe Unit of randomization (eg, individual, cluster, geographic).[15] Method used to generate the allocation schedule.[16] Method of allocation concealment and timing of assignment.[17] Method to separate the generator from the executor of assignment.[17,18]		
	Masking (Blinding)	Describe mechanism (eg, capsules, tablets); similarity of treatment characteristics (eg, appearance, taste); allocation schedule control (location of code during trial and when broken); and evidence for successful blinding among participants, person doing intervention, outcome assessors, and data analysts.[19,20]		
Results				
	Participant Flow and Follow-up	Provide a trial profile (Figure) summarizing participant flow, numbers and timing of randomization assignment, interventions, and measurements for each randomized group.[3,21]		
	Analysis	State estimated effect of intervention on primary and secondary outcome measures, including a point estimate and measure of precision (confidence interval).[22,23] State results in absolute numbers when feasible (eg, 10/20, not 50%). Present summary data and appropriate descriptive and inferential statistics in sufficient detail to permit alternative analyses and replication.[24] Describe prognostic variables by treatment group and any attempt to adjust for them.[25] Describe protocol deviations from the study as planned, together with the reasons.		
Comment		State specific interpretation of study findings, including sources of bias and imprecision (internal validity) and discussion of external validity, including appropriate quantitative measures when possible. State general interpretation of the data in light of the totality of the available evidence.		



Progress through the various stages of a trial, including flow of participants, withdrawals, and timing of primary and secondary outcome measures. The "R" indicates randomization.

selection of checklist items: implications for biobank

- evidence-based, whenever possible
  - not reporting the item, compared to reporting it, induced bias
    - e.g., allocation concealment

evidence

- title

- identify the study as a randomized trial
  - electronic searching of Medline yield < 50% of relevant trials

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309:1286-1291

evidence

- abstract

- use a structured format
  - compared the quality of structured abstracts to unstructured ones
  - 3 journals prior to and after the introduction of structured abstracts (57% versus 73%)

Taddio A, Pain T, Fassos FF, Boon H, Illersich AL, Einarson TR. Quality of nonstructured and structured abstracts of original research articles in the British Medical Journal, the Canadian Medical Association Journal and the Journal of the American Medical Association. Canadian Medical Association Journal 1994;150:1611-1615

dissemination

- all the major general & internal medicine journals endorse CONSORT
  - require authors to submit RCT reports using CONSORT template
- editorial groups that have endorsed CONSORT
  - world association of medical editors (wame)
  - council of science editors (cse)
  - international committee of medical journal editors (vancouver group)

changing behavior: a system change

- regulations put in place
  - modification of ‘instructions to authors’ section of journal
  - editorial as to what journal is going to do

revising the CONSORT statement

to deal with criticism of the original statement
and incorporate emerging evidence

additions to the CONSORT statement

- only 119 of 249 reports of RCTs mentioned intention-to-treat analysis
- reporting an intention to treat analysis was associated with some other aspects of good study design and reporting, such as describing a sample size calculation

Hollis S Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 1999;319:670-674

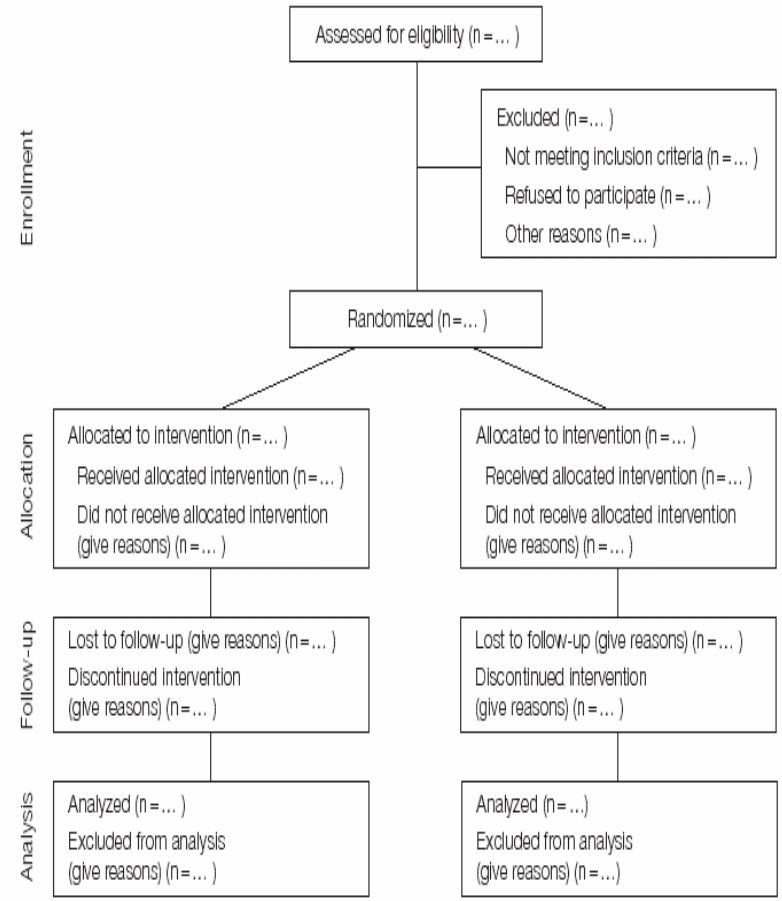
Ruiz-Canela M, Martínez-González MA, de Irala-Estévez J. Intention to treat analysis is related to methodological quality. BMJ 2000;320:1007-1008

- Moher D, Schulz KF, Altman DG, for the CONSORT group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials.
  - annals of internal medicine 2001;134:657-662
  - lancet 2001;357:1191-1194
  - jama 2001;285:1987-1991.

Table. Checklist of Items to Include When Reporting a Randomized Trial

Section and Topic	Item #	Descriptor	Reported on Page #
Title and Abstract	1	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned").	
Introduction			
Background	2	Scientific background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization			
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat." State the results in absolute numbers when feasible (eg, 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (eg, 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
Comment			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

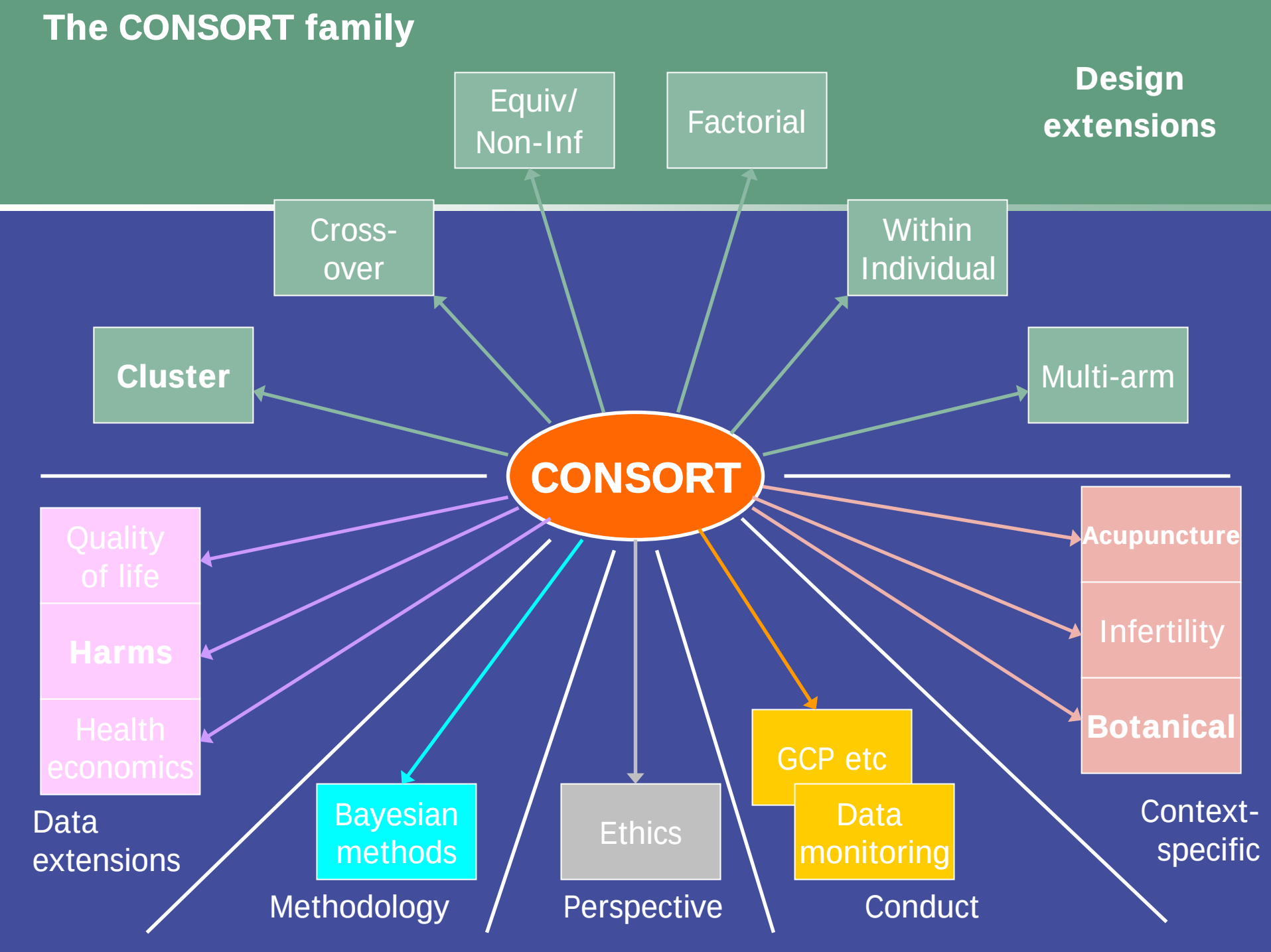
Figure. Flow Diagram of Subject Progress Through the Phases of a Randomized Trial



development of the explanation and elaboration manuscript: implications for biobank

- to enhance the use and dissemination of CONSORT
- format
  - checklist item
  - examples
  - explanation
    - patterned after the icmje's "uniform requirements for manuscripts submitted to biomedical journals"

Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T, for the CONSORT group. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. annals of internal medicine 2001;134:663-694


The CONSORT family
Design extensions
Equiv/ Non-Inf
Factorial
Cross-over
Within Individual
Cluster
Multi-arm
CONSORT
Quality of life
Harms
Health economics
Data extensions
Bayesian methods
Methodology
Ethics
Perspective
GCP etc
Data monitoring
Conduct
Acupuncture
Infertility
Botanical
Context-specific

improving the quality of reporting for randomized controlled trials evaluating herbal interventions: an *extension (or implementation)* of the CONSORT Statement

Gagnier JJ, Boon H, Rochon P, Barnes J, Moher D, Bombardier C, for the CONSORT Group

Standard CONSORT checklist: Paper Section and Topic	Standard CONSORT checklist: Item	Description	Reported on Page number
TITLE & ABSTRACT	1	How participants were allocated to interventions (e.g., "random allocation," "Randomized" or "randomly assigned"). *Either the title or abstract, or both should state the herbal medicinal product's Latin binomial, the part of the plant used, and the type of preparation.*	
INTRODUCTION Background	2	Scientific background and explanation of the rationale. *This should include briefly stated reasons for the trial with reference to the specific herbal medicinal product being used in the study. If applicable, whether new or traditional indications are being tested.*	
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected. *If a traditional indication is being tested the authors must describe how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication.*	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered. *A detailed extension of this item is outlined in table 2.*	
Objectives	5		
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). *Outcome measures should reflect the intervention and indications tested considering, where applicable, underlying theories and concepts.*	
Sample size	7		
Randomization Sequence allocation	8		
Allocation concealment	9		
Implementation	10		
Blinding (Masking)	11		
Statistical methods	12		
RESULTS Participant flow	13		
Recruitment	14		
Baseline data	15	Baseline demographic and clinical characteristics of each group. *Including, concomitant medication use or herbal medicinal product use.*	
Numbers analyzed	16		
Outcomes and Estimation	17		
Ancillary analyses	18		
Adverse events	19		
DISCUSSION Interpretation	20	Interpretation of results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes. *Interpretation of the results in light of the product and dosage regimen used.*	
Generalizability	21	Generalizability (external validity) of trial results. *Where possible, discuss how the herbal product used relates to what is used in self-care and/or practice.*	
Overall evidence	22	General interpretation of the results in the context of current evidence. *Discussion of the trial results in relation to trials of other available products.*	

Table 1: Proposed Extensions for Randomized Controlled Trials of Botanical Medicine

Standard CONSORT checklist: Paper Section and Topic	Standard CONSORT checklist: Item	Descriptor	Reported on Page number
TITLE & ABSTRACT	1	How participants were allocated to interventions (e.g., "random allocation," "Randomized" or "randomly assigned"). *Either the title or abstract, or both should state the herbal medicinal product's Latin binomial, the part of the plant used, and the type of preparation.*	
INTRODUCTION Background	2	Scientific background and explanation of the rationale. *This should include briefly stated reasons for the trial with reference to the specific herbal medicinal product being used in the study. If applicable, whether new or traditional indications are being tested.*	
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected. *If a traditional indication is being tested the authors must describe how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication.*	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered. *A detailed extension of this item is outlined in*	

implementation (rather than extension): implications for biobank

Table 2: Proposed Extensions of CONSORT Item 4 for Randomized Controlled Trials of herbal Medicines

Standard CONSORT checklist: Paper Section and Topic	Standard CONSORT checklist: Item	Descriptor	Reported on Page number
METHODS Interventions	4.	Precise details of the interventions intended for each group and how and when they were actually administered. *Where applicable, the description of a herbal intervention should include:*	
	4.A Herbal medicinal product name	*1. The Latin binomial and common name/names together with authority and family name*	
		2. The proprietary product name (i.e. brand name) or the extract name (e.g. LI160) and the manufacturer of the product	
		3. Whether the product used is licensed	
	4.B. Characteristics of the herbal product	*1.The part(s) of plant contained in the product or extract.*	
		2.The type of product used [e.g. raw (fresh or dry), extract]	
		3.The type and concentration of extraction solvent used (e.g. 80% Alcohol, H_20 100%, 90% glycerine etc.) and the plant to plant extract ratio (plant:plant extract; e.g. 2:1)	
		4.The method of authentication of raw material (i.e. how done and by whom) and the lot number of the raw material.	

- developing and e and e document
- as did STARD
  - Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HCW for the STARD group. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Explanation and Elaboration. Annals of Internal Medicine 2003;138:W1-W12
- as will QUOROM and STROBE

does CONSORT work?
implications for biobank

does journal endorsement of the CONSORT statement (checklist) improve the quality of reports of randomized controlled trials?

evaluations of CONSORT: checklist

- Moher D, Jones A, Lepage L for the CONSORT group. Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *JAMA* **2001**;285(15):1992-1995.
- **Devereaux PJ, Manns BJ, Ghali WA, Quan H, Guyatt GH. The reporting of methodological factors in randomized controlled trials and the association with a journal policy to promote adherence to the Consolidated Standards of Reporting Trials (CONSORT) checklist. *Control Clin Trials* 2002;23(4):380-388.**
- Stinson JN, McGrath PJ, Yamada JT. Clinical trials in the Journal of Pediatric Psychology: applying the CONSORT statement. *J.Pediatr.Psychol.* 2003;28(3):159-167.
- Faunce TA, Buckley NA. Of consents and CONSORTs: reporting ethics, law, and human rights in RCTs involving monitored overdose of healthy volunteers pre and post the "CONSORT" guidelines. *J.Toxicol.Clin.Toxicol.* **2003**;41(2):93-99.
- Piggott M, McGee H, Feuer D. Has CONSORT improved the reporting of randomized controlled trials in the palliative care literature? A systematic review. *Palliat.Med.* **2004**;18(1):32-38.

Devereaux PJ, Manns BJ, Ghali WA, Quan H, Guyatt GH. The reporting of methodological factors in randomized controlled trials and the association with a journal policy to promote adherence to the Consolidated Standards of Reporting Trials (CONSORT) checklist. *Control Clin Trials* 2002;23(4):380-388.

- **methodology**
  - 105 reports of rcts published in 29 journals of which 10 explicitly endorsed CONSORT and 16 did not
  - time-frame: 1997 (median)
  - used an 11-item checklist adapted from the 1996 CONSORT checklist
  - trained assessors to complete checklist

results and interpretation

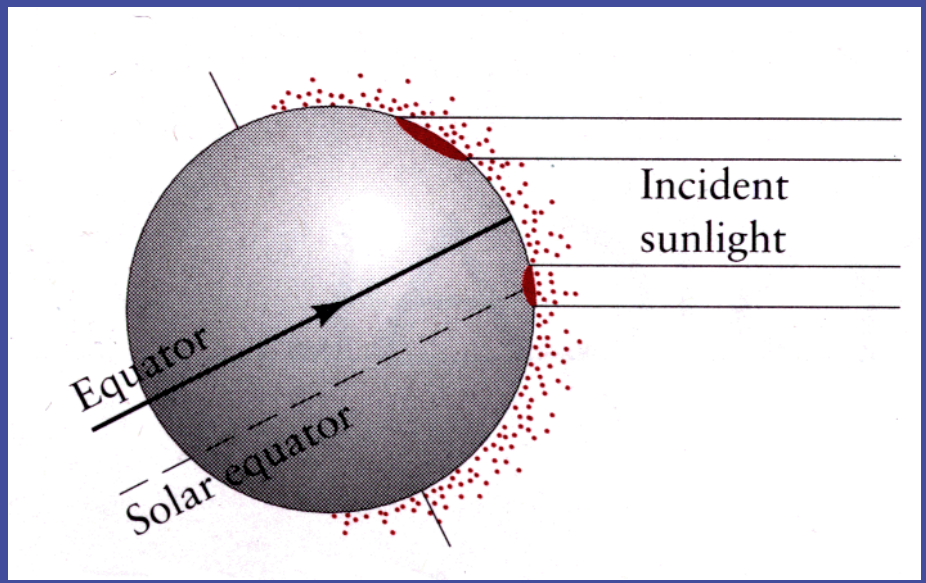
- 6 (of 11) methodological items were reported <50 of the time
- quality of reporting rcts is far from perfect
- the number of items reported was statistically greater in CONSORT adopters than corresponding control journals

ESCORT **working group**

continual review and updating of CONSORT is essential:
implications for biobank

***E*vidence *S*upporting (or refuting!) the *C*ONSORT *S*tandards *O*n *R*eporting *T*rials**

EQUATOR - **Excellence in the QUAlity of Trials and Other Research: implications for biobank**



- commonality of evidence base
  - e.g., funding source
- commonality of approach
  - funding sources
- ear of editors
- broad dissemination

tips to consider when developing a biobank reporting guidance (i)

- need to develop the evidence-base
  - e.g., Ioannidis
- need to fund the development of an evidence base
- need to hold ‘international’ meeting with representation from across geographical regions
  - need to check egos at door!
- need to involve (from the beginning) influential journal editors

tips to consider when developing a biobank reporting guidance (ii)

- need to produce ‘statement’
  - extension or implementation (of STROBE)
  - embrace the kiss principle
  - need to develop an ‘e and e’ document
- publish statement in several journals simultaneously
  - publish e an e document simultaneously

tips to consider when developing a biobank reporting guidance (iii)

- keep the statement up to date
  - monitor the literature constantly
- evaluate its effectiveness
- create a website
- fund the initiative!

come and visit ottawa!